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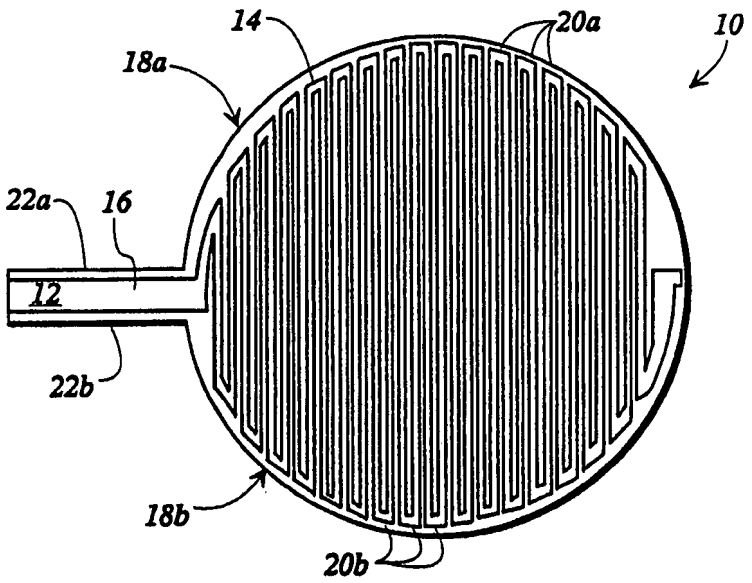

(57) Abstract

A method of delivering topical drugs to the tissue includes the step of applying the drug to be delivered to one of an area of tissue to be treated and an electrode device (10). The electrode device, which is formed to generate a multiplicity of simultaneous and directionally distinct electrical fields, is then placed in contact with the area of tissue to be treated. Voltage is delivered to the electrode device to generate simultaneous and directionally distinct electric fields at the tissue surface.

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METHOD AND APPARATUS FOR TREATING TISSUE

Field of the Invention

This invention relates to a novel method and apparatus for treating tissue, including the application of an electric field to tissue surfaces as well as the delivery of topical drugs to an area of tissue to be treated using such electric field. More specifically, the invention relates to methods of delivering topical drugs, including proteins and nucleic acids, to skin by electrically stimulating the skin. Further, the invention relates to the transdermal delivery of electrical stimulation across the skin boundary to treat the underlying tissue. Such treatment can include the delivery of a drug or other compound to such tissue.

Background

Iontophoresis is a well known technique for delivering drugs through the skin which involves applying an electric potential gradient at the skin surface to enhance the permeability of the skin to the drug molecules. Research has been conducted on iontophoretic transdermal delivery of

peptide and protein drugs (Chien, Yie W., et al., (1989) J. of Pharm. Sci. 78, 376-383); nonpeptide drugs (Sanderson, et al., (1989) J. of Pharm. Sci. 78, 361-364); and polypeptide drugs (Srinivasan, V., et al., (1989) J. of Pharm. Sci. 78, 370-375).

Iontophoresis has proven effective for transdermal delivery of local anesthesia, metallic and nonmetallic ions, vasodilators, dermatological medications, and steroids (Behl, et al. (1989) J. of Pharm. Sci. 78, 355-360). One of the earliest uses of iontophoresis involved introducing a sweat-inducing drug through the skin to diagnose cystic fibrosis (Chien, Yie W., et al. (1989) J. of Pharm. Sci. 78, 353-354). Other biomedical applications of iontophoresis include treatment for hyperhidrosis, edema formation, calcium deposits, and hay fever (Behl, et al., (1989) J. of Pharm. Sci. 78, 355-360).

An iontophoretic drug delivery system generally includes a power source, control circuitry, and two electrode pads. One of the electrode pads contains a solution of an ionic drug and the other electrode pad contains an electrolyte. To effect delivery of the drug, the electrode pads are placed on the skin, and an electric current is supplied to the pads to induce an electric field at the skin surface. The power supply is connected to the electrode pads so that the charge of the pole connected to the drug-containing electrode is the same as the charge of the ionic drug. The application of an electric potential at the drug-containing electrode will drive the drug ions through the skin and into the body (Sanderson, John E. et al. (1987) J. of Pharm. Sci. 76, 215-218; Phipps, J. B., et al. (1989) J. of Pharm. Sci. 78, 365-369).

One such iontophoretic drug delivery system, marketed by Iomed, Inc. under the trademark TransQl, includes a dispersive electrode and a drug delivery electrode. The drug delivery electrode is mounted to a plastic holding

tray which includes an absorbent pad for receiving the drug. Once the pad is fully hydrated with the drug, the drug delivery electrode and absorbent pad are separated from the holding tray and placed on the skin at the treatment site. The dispersive electrode is placed on the skin spaced from the drug delivery electrode, and leads are attached to the pair of electrodes to generate an electric potential gradient at the treatment site. This drug delivery system is primarily used to deliver a water soluble medication, such as a local anesthetic and/or corticosteroid, through a patient's skin. A disadvantage of this system is the excessive length of time required for treatment.

Rogaine (Minoxidil, 2% topical solution) is a topically applied drug, marketed by the Upjohn Company, which has proven effective in treating male pattern baldness involving the top, or vertex, of the head. Although Rogaine has successfully stimulated hair growth on the top of the head, no clinically significant effect has been seen in patients with predominantly frontal hair loss.

Accordingly, it is therefore a general object of the invention to provide methods of treating the surface of tissue with an electric field.

It is a specific object of the invention to provide methods of applying a topical drug to a tissue which increases the efficiency and effectiveness of the drug.

It is a further specific object of the invention to provide a method of applying Rogaine to the frontal lobes of a user's head which stimulates detectable hair growth.

It is another object of the invention to provide an electrode device for use with the subject method which is sterile, disposable, noninvasive, pain free, easy to manufacture, and inexpensive to mass produce.

Disclosure of the Invention

A preferred method of delivering topical drugs to the skin which is intended to accomplish at least some of the foregoing objects includes the step of applying the drug to be delivered to one of an area of skin to be treated and an electrode device. In a preferred embodiment, the drug is applied to the electrode device. The electrode device, which is formed to generate a multiplicity of simultaneous and directionally distinct electrical fields, is then placed in contact with the area of skin to be treated. Finally, voltage is delivered to the electrode device to generate simultaneous and directionally distinct electric fields at the skin surface.

Such methods and apparatus may be readily applied to similar treatment of other tissue surfaces. Further, such methods and apparatus may be readily adapted to apply unique electric fields to the surface of tissue and to tissue underlying such tissue surfaces to enhance circulation or the delivery of drugs to such tissue.

Brief Description of the Drawings

Other objects and advantages of the present invention will become apparent from the following detailed description of a preferred embodiment thereof taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is a top plan view of an electrode device for use with the subject method of delivering topical drugs to the skin;

FIGURE 2 is an enlarged top view of a section of the electrode device of Figure l; and

FIGURES 3a-c are photographs of enhanced hair growth using the methods and apparatus of the invention.

Best Mode of Carrying Out the Invention

Before describing the subject methods of applying novel electric fields and the delivery of drugs to a tissue surface or underlying tissue, it may be helpful to describe the electrode device for use with the subject method. Referring to the drawings, wherein like numerals indicate like parts, and initially to FIGURE 1, there will be seen an electrode device 10 including a substantially planar support member 12 composed of a substantially non-conductive material. This device in general is made of a flexible planar support member to accommodate the contours of the tissue surface to be treated. Suitable non-conductive materials for forming support member 12 include mica, polyester, and polystyrene. Support member 12 has a main portion 14, preferably circular in shape, and a tab portion 16 extending from the perimeter of main portion 14. Tab portion 16 facilitates connection of lead lines to electrode device 10.

A first electrode pattern 18a and a second electrode pattern 18b are disposed on main portion 14 of electrode device 10. First electrode pattern 18a and second electrode pattern 18b each include a set of substantially parallel electrodes 20a and 20b, respectively, which extend across main portion 14 in an alternating arrangement. Electrodes 20a and 20b are uniformly spaced across main portion 14 to ensure an even distribution of current density beneath electrode device 10, thereby reducing the likelihood of skin burns.

A pair of electrode leads 22a and 22b extend along opposite sides of tab portion 16 and halfway around the

perimeter of main portion 14. Electrodes 20a are electrically coupled together by electrode lead 22a, and electrodes 20b are electrically interconnected by electrode lead 22b. Each set of electrodes 20a and 20b are electrically connected to one another so that a voltage applied to the corresponding electrode leads 22a and 22b is uniformly distributed across each of the electrodes.

The alternating arrangement of first and second electrode patterns 18a and 18b, respectively, generates multiple directionally distinct electrical fields when opposite charges are applied to electrode leads 22a and 22b. Turning to FIGURE 2, the arrows represent electric field lines generated by connecting lead lines of opposite polarity to electrode leads 22a and 22b.

Although a preferred embodiment of support member 12 is circular in shape, support member 12 may be fabricated in different shapes according to the area of tissue to be treated and according to the specific medical application.

Electrode patterns may be formed by screen printing a conductive ink on support member 12. A technique for printing a conductive ink on a flexible substrate is disclosed by M. Martel in "The Basics of Area Source IR", SITE Magazine, pgs. 60-64. Suitable conductive inks for forming the electrode patterns of the subject invention include E-1400 ink marketed by Ercon Incorporated and Electrodag PTF inks marketed by Acheson Colloids Company.

Alternatively, the electrode patterns may be formed by selectively depositing a metallic material, such as aluminum, on main portion 14. Or, the electrode patterns may be formed by using a masking technique to deposit copper vapor or other metallic vapor such as aluminum, gold, platinum, and nickel, on main portion 14.

The methods used to produce such vapor deposited electrode devices and selectively etched electrode devices are well known. Metal deposition may be carried out according to the methods disclosed by P. Gise and R. Blanchard in "Modern Semiconductor Fabrication Technology", Chapter 8 (Prentice-Hall, England Cliffs, New Jersey, 1986), and A.B. Glaser and G.E. Subak-Sharpe in "Integrated Circuit Engineering", Chapter 5 (Addison-Wesley, Reading, Massachusetts, 1977) and selective etching of laminated material may be carried out according to the methods disclosed by C.F. Coombs, Jr., ed., in "Printed Circuit Handbook", Chapters 1 and 8 (McGraw-Hill, New York, New York, 1976).

The electrode material preferably ranges in thickness from approximately .001 inches to 1 inch. Each electrode has a width of approximately 10μm to 2mm, preferably between 0.1mm and 1mm. The spacing between the electrodes ranges from approximately 10μm to 2mm, preferably 0.1mm to 1mm.

Since these electrodes are positioned close together, a user may apply a relatively low voltage across first and second electrode leads 22a and 22b to generate an appropriate voltage gradient or sufficient electrical current. In most applications, 10 to 100 volts DC are applied across electrode leads 22a and 22b; however, the applied voltage may range from approximately 1 to 500 volts DC. It is preferable to deliver a pulsed voltage, as opposed to a continuous voltage, to electrode device 10 to prevent the build-up of charge on the skin.

The subject method for delivering a topical drug to tissue will now be described. According to the subject method, a topical drug is applied to one of an area of tissue to be treated and electrode device 10. Tissue includes but is not

limited to skin, tendons, muscles, nerves, internal organs and tissues of the oral cavity. In a preferred embodiment, the drug is applied to a localized area of skin to ensure even distribution of the drug across the skin surface. If the drug is applied directly to electrode device 10, the drug should be spread evenly across the surface of device 10 on which electrode patterns 18a and 18b are disposed, or the conductive surface of device 10. Once the drug has been applied, the conductive surface of device 10 is placed in contact with the area of skin to be treated. A voltage is then applied across electrode leads 22a and 22b to generate simultaneous and directionally distinct electric fields between electrodes 20a and 20b. The electric fields electrically stimulate the area of skin being treated. Although the exact mechanism is unknown, it is believed that application of electric fields to the skin surface enhances the permeability of the skin to the topical drug, thereby increasing the absorption of the drug through the skin. The increased absorption contributes to an increase in the efficiency and effectiveness of the drug delivery.

The subject method of the invention may be used in combination with the topical hair growth drug Rogaine, commercially marketed by The Upjohn Company. Previously, Rogaine has only been successful in promoting hair growth on the vertex of the head. However, when used in combination with electrode device 10, Rogaine has been shown to stimulate hair growth on the front of the scalp. According to the subject method, a user applies a full dose of Rogaine, specifically lmL, to the front of the scalp per the directions found in the literature accompanying a Rogaine prescription. After the full dose has been applied to the user's scalp with the supplied rub-ON applicator, the user places the conductive surface of electrode device 10 in contact with the area of the scalp to be treated. The user then turns on the power supply to electrode device 10 which is preferably set to deliver approximately fifty to one hundred 100 volt DC pulses of 1 ampere of

current over a period of 15 to 30 seconds, each pulse lasting approximately 1 to 10 msec. As the pulses are being applied to electrode device 10, the user may move electrode device 10 over the area of skin being treated. The user may selectively apply pressure to electrode device 10 to adjust the contact of electrode device 10 with the skin. During treatment, the user may feel a sensation of mild tingling. After approximately four months of treatment, hair growth becomes apparent. This was repeated twice daily over 60 days.

The results of applying Rogaine to the frontal lobe of the scalp and treating the scalp with the electrode device as described above over a 60 day period are shown in FIGURES 3a-c. FIGURE 3a shows the condition of the scalp on day 0 prior to the start of the experiment. FIGURES 3b and 3c show the same scalp after 20 and 60 days, respectively. The right side of the scalp (left side in the figures) is the area treated with Rogaine and the electrode device 10. The left side of the scalp (right side in the figures) is the control area, i.e., treated only with Rogaine. In FIGURE 3b, new hair growth is seen at 20 days. As is also apparent in FIGURE 3c, hair growth after just 60 days was substantial.

The subject electrode device 10 may also be used in combination with other topical drugs to treat a variety of skin maladies including: (i) Retin A (Tretinoin, all, trans Retinoic Acid), commercially marketed by Ortho Pharmaceuticals, for treatment of brown spots, acne, and wrinkles, (ii) steroids to treat inflammation and psoriasis, (iii) topical pain relievers for treatment of aberrations of the skin and underlying tissue, and (iv) 5-fluorouracil to treat skin cancer and psoriasis.

In addition to delivering drugs to a localized area of skin and skin tissue, electrode device 10 may also be used without an accompanying topical drug. Electrical stimulation

alone has therapeutic and diagnostic value. Electrode device 10 may be used to electrically stimulate the skin of a user to, for example, increase blood flow, induce secretions, and stimulate nerves.

As an example, tests were performed where the electrode device 10 was applied to the inner forearm area of a human. The same protocol as previously described was used except no topical drug was applied to the skin or electrode device 10. The test produced a region of redness indicating increased circulation to the area. The increased circulation is useful for enhancing the delivery of drugs to the localized skin area which are administered IV or orally.

An advantage of using the apparatus and method of the invention lies in the fact that treatment can be effected without significant discomfort of tissue damage (even after twice daily treatment for almost six months). The only feeling sensed by the user is a mere tingling of the scalp which is believed to be evidence of subcutaneous nerve stimulation.

Electrode device 10 may also provide gene therapy to skin or other tissue by transfecting nucleic acid into the cells of the skin or tissue or cells underlying such surfaces for treating gene deficiencies or inducing such deficiencies in laboratory animals. Nucleic acids which may be used for transfection include DNA capable of expressing an antisense RNA transcript which is capable of down modulating translation of endogenous RNA transcripts. Proteinaceous gene products may also be delivered to the skin cells by the subject method. Such proteins include Factor VIII, insulin, and adenosine deaminase.

In describing the invention, reference has been made to a preferred embodiment and illustrative advantages of the invention. Those skilled in the art, however, and familiar with the instant disclosure of the subject invention, will

recognize additions, deletions, modifications, substitutions, and other changes which will fall within the purview of the subject invention and claims.

CLAIMS

What is claimed is:

1. A method for delivering topical drugs to tissue comprising the steps of:

applying the drug to be delivered to one of an area of tissue to be treated and an electrode device formed to generate a multiplicity of simultaneous and directionally distinct electric fields;

placing said electrode device in contact with the area of tissue to be treated; and

delivering voltage to said electrode device to generate a multiplicity of directionally distinct electrical fields at the tissue surface to electrically stimulate the area of tissue being treated.

2. A method as defined in claim 1 wherein:

said electrode device includes a flexible, nonconductive, substantially planar support member; and

first electrode means and second electrode means each including at least two electrically connected, substantially parallel electrodes, said first electrode means and said second electrode means arranged on a planar surface of said electrode device so that the electrodes of said first electrode means alternate with the electrodes of said second electrode means and, upon connection to said power supply, said electrode device generates said multiplicity of directionally distinct electric fields between the electrodes of said first electrode means and the electrodes of said second electrode means.

3. A method as defined in claim 1 wherein:

said applying step is accomplished by coating the area of tissue being treated with the drug.

4. A method as defined in claim 1 further comprising the step of:

after delivering said step, moving said electrode device over the area of tissue being treated.

5. A method as defined in claim 1 further comprising the step of:

after said delivering step, applying selective pressure to said electrode device to adjust contact of said electrode device with the area of tissue being treated.

6. A method as defined in claim 1 wherein:

said delivering step is accomplished by connecting a power supply to said electrode device to deliver a pulsed voltage to said electrode device.

7. A method as defined in claim 6 wherein:

said power supply delivers approximately 50 to 100 voltage pulses over approximately 15 to 30 seconds to said electrode device.

8. A method as defined in claim 7 wherein:

said power supply is set to deliver voltage pulses of approximately 100 volts at about 1 ampere, each having a duration approximately 1 to 10 msec.

9. A method as defined in claim 1 wherein:

said delivering step is accomplished by connecting a power supply to said electrode device to deliver a continuous voltage to said electrode device.

10. A method as defined in claim 1 wherein:

said electrode device is formed in the shape of the area of tissue to be treated.

11. A method as defined in claim 2 wherein:

said second electrode means are formed by conductive inks.

12. A method of providing electrical stimulation to tissue comprising the steps of:

placing an electrode device in contact with the tissue, said electrode device formed to generate a multiplicity of directionally distinct electric fields, and delivering voltage to said electrode device to generate a multiplicity of simultaneous and directionally distinct electric fields at the tissue surface to electrically stimulate the tissue.

13. A method as recited in claim 12, wherein said tissue stimulated by said electrode device is skin.

14. A method of stimulating hair growth on the head of a user comprising the steps of:

applying a hair growth drug to an area of skin to be treated;

placing an electrode device in contact with the area of skin to be treated, said electrode device formed to generate a multiplicity of simultaneous and directionally distinct electric fields; and

delivering voltage to said electrode device to generate a multiplicity of directionally distinct electric fields at the skin surface to electrically stimulate the area of skin being treated.

15. A method as defined in claim 14 wherein:

said applying step is accomplished by spraying said hair growth drug on the frontal portion of a user's head.

16. A method as defined in claim 14 wherein:

said applying step is accomplished by rubbing said hair growth drug on the frontal portion of a user's head.

17. An electrical stimulation apparatus comprising:

a substantially planar support member having a substantially non-conductive surface, in contact with a tissue surface;

first electrode means comprising at least two electrically-connected substantially parallel electrodes disposed on said substantially non-conductive surface; and

second electrode means comprising at least two electrically-connected substantially parallel electrodes also disposed on the same surface as said first electrode means such that the electrodes of said first and second electrode means are alternately positioned on said surface.

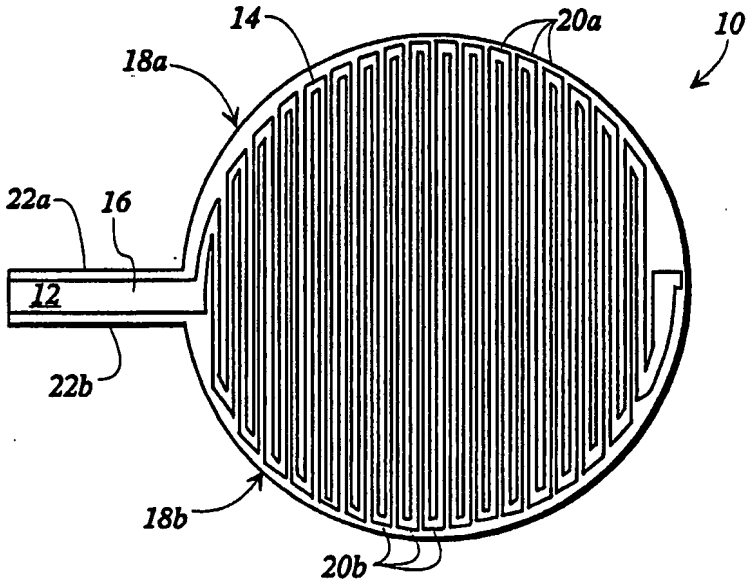

FIG 1

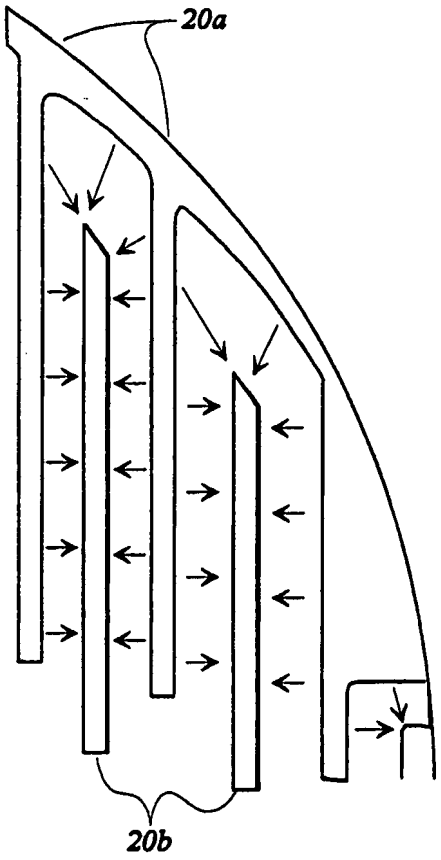

FIG 2

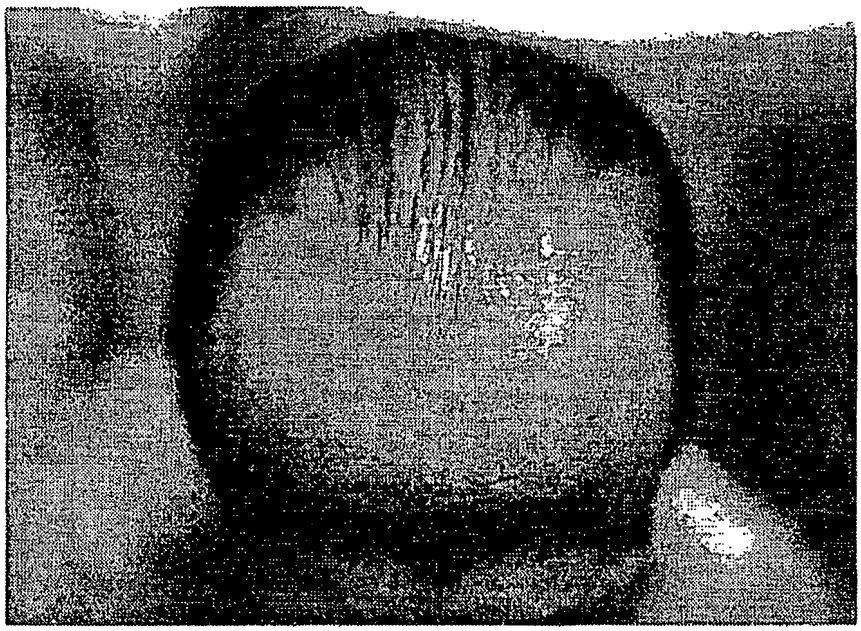

FIGURE 3A

DAY 0

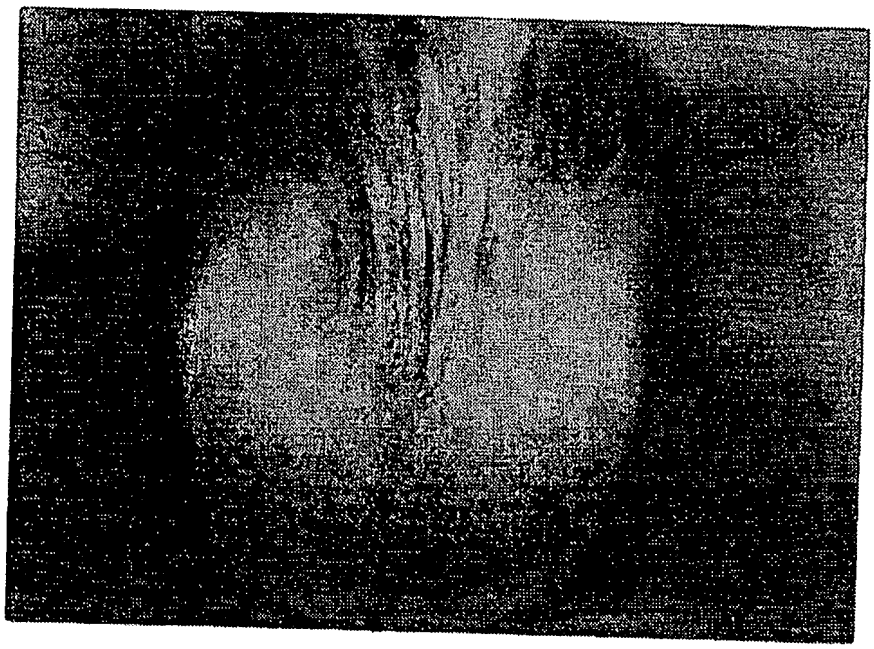

FIGURE 3B

DAY 20

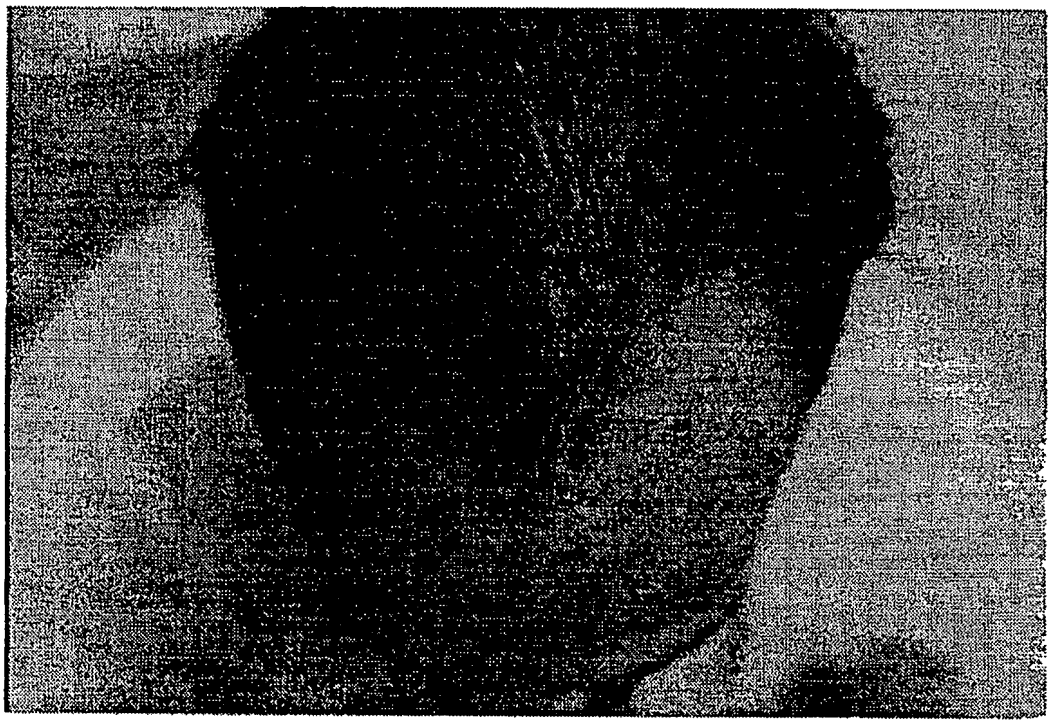

FIGURE 3C

DAY 60

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05587

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61N 1/30
US CL :604/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/798,799,802,803

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,164,226 (TAPPER) 14 August 1979, See figure 4.	12,13,17 1-11,14-16
Y	US, A, 4,736,752 (MUNCK ET AL.) 12 April 1988, See Abstract.	11
X	US, A, 5,002,527 (RELLER ET AL.) 26 March 1991, See Abstract, Figure 1.	1,2,6,9
Y	GB, A, 2,132,892 (HAYASHIBARA) July 1984, See Abstract.	14-16
Y	DE, A, 3,736,072 (COHAUSZ ET AL.) 13 April 1989.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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